Clinical trial results:
A multicenter, Double-blind, RandOmised, two arm Parallel group trial to determine the effects of torasemide versus furosemide on one marker (PIP) of cardiac fibrosis in patient with Diastolic Heart Failure and diabetes mellitus type II

Summary

EudraCT number	2013-003601-25
Trial protocol	DE
Global end of trial date	20 September 2016

Results information

Result version number	v1 (current)
This version publication date	17 March 2022
First version publication date	17 March 2022

Trial information

Trial identification

Sponsor protocol code	DROP-PIP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Augustenburger Platz 1, Berlin, Germany, Augustenburger Platz
Public contact	Prof. Dr. Carsten Tschöpe, Charité Universitätsmedizin Berlin, 49 30450 553712, Carsten.Tschoepe@charite.de
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to determine whether torasemide is superior to furosemide in reducing one marker (PIP) of cardiac fibrosis in subjects with diastolic heart failure and diabetes type II.

Protection of trial subjects:

Qualified personnel monitored the trial, performed off- and on-site visits and assured scientific integrity. A control contact by phone after 44 days, a control visit after 5 months, a final visit for blinded PIP measurements, and secondary endpoint assessment after 9 months. For safety, we followed up the patients 2 weeks after the final visit.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patient enrollment started 1 October 2014 and ended by 21 December 2015. Consecutive, eligible subjects meeting inclusion/exclusion criteria were considered for the study. The investigators verified that patients met all inclusion. Patients with PIP measurements >=110 ng/mL or >=70 ng/mL with LAVI .29 mL/m2 at screening were eligible for randomis

Pre-assignment

Screening details:

A total of 214 patients were pre-screened, 51.4% declined to participate in DROP-PIP. Out of the 104 patients undergoing full screening, 14% had elevated PIP levels (≥110 ng/mL), and 54% of patients showed abnormal serum PIP levels in the grey zone of <110 ng/mL and ≥70 ng/mL.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

Patients, the investigator team,
individuals performing the assessments, and data analysts remained
blinded to the identity of treatment until after database lock;

Arms

Are arms mutually exclusive?	Yes
Arm title	Furosemide Group

Arm description:

Patients were supplied with the drug at specified visits during the
treatment period and received sufficient supply of the study drug to
last until their next scheduled visit.

Arm type	Active comparator
Investigational medicinal product name	Furosemid
Investigational medicinal product code	Furosemid
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

furosemide 20 mg:
Patients were supplied with the drug at specified visits during the
treatment period and received sufficient supply of the study drug to
last until their next scheduled visit.

Arm title	Torasemide Group

Arm description:

The investigators dispensed the
study drug to the subject after the appropriate treatment allocated
for the subject via randomisation and according to the protocol.

Arm type	Experimental
Investigational medicinal product name	Torasemid
Investigational medicinal product code	Torasemid
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5mg Torasemide
Patients were supplied with the drug at specified visits during the treatment period and received sufficient supply of the study drug to last until their next scheduled visit.

Number of subjects in period 1	Furosemide Group	Torasemide Group
Started	18	17
Completed	16	12
Not completed	2	5
Adverse event, serious fatal	1	-
Lost to follow-up	-	1
Protocol deviation	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Furosemide Group
Reporting group description:	
Patients were supplied with the drug at specified visits during the treatment period and received sufficient supply of the study drug to last until their next scheduled visit.	
Reporting group title	Torasemide Group
Reporting group description:	
The investigators dispensed the study drug to the subject after the appropriate treatment allocated for the subject via randomisation and according to the protocol.	

Reporting group values	Furosemide Group	Torasemide Group	Total
Number of subjects	18	17	35
Age categorical			
Units: Subjects			
Adults ≥18 years	18	17	35
Age continuous			
Units: years			
arithmetic mean	69.3	68.0	
standard deviation	± 8.1	± 8.3	-
Gender categorical			
Units: Subjects			
Female	11	4	15
Male	7	13	20
Peripheral oedema			
Units: Subjects			
Peripheral oedema (yes)	17	15	32
Peripheral oedema (No)	1	2	3
Pulmonary congestions			
Units: Subjects			
Pulmonary congestions (yes)	5	3	8
Pulmonary congestions (no)	13	14	27
New York Heart Association			
NYHA			
Units: Subjects			
class I	4	2	6
class II	6	10	16
class III	8	5	13
Heart rate			
Units: b.p.m			
arithmetic mean	74.8	72.3	
standard deviation	± 19.2	± 15.5	-
Systolic BP			
Units: mmHg			
arithmetic mean	136.8	130.2	
standard deviation	± 19.2	± 17.2	-
Diastolic BP			

Units: mmHg			
arithmetic mean	76.8	74.0	
standard deviation	± 9.9	± 12.3	-
Body mass index			
Units: kg/m2			
arithmetic mean	34.8	34.5	
standard deviation	± 6.3	± 6.7	-
Respiratory rate			
Units: /min			
arithmetic mean	17.1	17.2	
standard deviation	± 1.8	± 1.4	-
Cardiac structure and function LVEF			
left ventricular ejection fraction (LVEF)			
Units: LVEF (%)			
arithmetic mean	62.5	61.0	
standard deviation	± 6.5	± 9.0	-
Cardiac structure and function LVMI			
Left ventricular mass index LVMI			
Units: LVMI (g/m²)			
arithmetic mean	116.1	129.6	
standard deviation	± 26.6	± 27.3	-
Cardiac structure and function LVEDVI			
left ventricular end diastolic ventricular volume index			
Units: LVEDVI (mL/m²)			
arithmetic mean	51.1	53.7	
standard deviation	± 14.0	± 18.4	-
Cardiac structure and function LAVI			
left atrial volume index LAVI			
Units: LAVI (mL/m2)			
arithmetic mean	37.8	42.7	
standard deviation	± 8.9	± 14.4	-
Cardiac structure and function E wave			
Units: m/s			
arithmetic mean	79.6	87.5	
standard deviation	± 19.5	± 20.8	-
Cardiac structure and function Deceleration time			
Units: time (ms)			
arithmetic mean	231.4	235.5	
standard deviation	± 74.8	± 59.9	-
Cardiac structure and function 6MWT			
6-minute walk test			
Units: distance (m)			
arithmetic mean	409.2	434.4	
standard deviation	± 110.2	± 127.6	-
Laboratory PIP			
C-terminal propeptide of procollagen type I			
Units: ng/mL			
arithmetic mean	133.1	99.7	
standard deviation	± 50.5	± 29.3	-
Laboratory Sodium			

Units: mmol/L			
arithmetic mean	141.8	141.1	
standard deviation	± 2.9	± 2.0	-
Potassium			
Units: mmol/L			
arithmetic mean	4.4	4.3	
standard deviation	± 0.4	± 0.5	-
Laboratory Creatinine			
Units: mg/dL			
arithmetic mean	1.00	1.0	
standard deviation	± 0.3	± 0.2	-
Laboratory eGFR			
eGFR: estimated glomerular filtration using the Modification of Diet in Renal Disease formula			
Units: mL/min			
arithmetic mean	70.7	73.5	
standard deviation	± 18.7	± 15.9	-
Laboratory NT-proBNP			
NT-proBNP: N-terminal pro-B-type natriuretic peptide			
Units: pg/mL			
arithmetic mean	148.2	201.8	
standard deviation	± 141.4	± 175.9	-
Quality of life KCCQ total symptom			
Kansas City Cardiomyopathy Questionnaire			
Units: score			
arithmetic mean	62.7	59.3	
standard deviation	± 28.7	± 26.6	-
Quality of life KCCQ clinical summary			
Kansas City Cardiomyopathy Questionnaire			
Units: Score			
arithmetic mean	62.9	58.1	
standard deviation	± 31.3	± 27.1	-
Quality of life KCCQ overall summary			
Kansas City Cardiomyopathy Questionnaire			
Units: Score			
arithmetic mean	61.5	56.6	
standard deviation	± 28.3	± 27.9	-

End points

End points reporting groups

Reporting group title	Furosemide Group
Reporting group description:	
Patients were supplied with the drug at specified visits during the treatment period and received sufficient supply of the study drug to last until their next scheduled visit.	
Reporting group title	Torasemide Group
Reporting group description:	
The investigators dispensed the study drug to the subject after the appropriate treatment allocated for the subject via randomisation and according to the protocol.	
Subject analysis set title	furosemide (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	
Primary and secondary outcomes were analysed in the per-protocol population.	
Subject analysis set title	torasemide (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	
Primary and secondary outcomes were analysed in the per-protocol population.	
Subject analysis set title	Diff (F–T) ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
difference between Furosemide and Torasemide	
Subject analysis set title	Diff (F-T) PP
Subject analysis set type	Per protocol
Subject analysis set description:	
difference between Furosemide and Torasemide in the per protocol group analysis	

Primary: Change of the PIP value PP

End point title	Change of the PIP value PP
End point description:	
End point type	Primary
End point timeframe:	
9 months	

End point values	furosemide (PP)	torasemide (PP)	Diff (F-T) PP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	16	12	28	
Units: ng/ml				
arithmetic mean (standard deviation)				
Percentage PIP change	3.08 (± 29.30)	3.72 (± 28.17)	-064 (± 28.83)	
Absolute PIP change	1.15 (± 38.11)	-1.25 (± 29.10)	2.40 (± 34.59)	

Statistical analyses

Statistical analysis title	change of the percentage in PIP values in PP
Comparison groups	furosemide (PP) v torasemide (PP)
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.27
upper limit	21.99

Statistical analysis title	change of the absolute values of PIP in PP
Comparison groups	torasemide (PP) v furosemide (PP)
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.75
upper limit	29.55

Secondary: Change of the Cardiac structure and function LVMI	
End point title	Change of the Cardiac structure and function LVMI
End point description: LVMI, left ventricular mass index	
End point type	Secondary
End point timeframe: 9 months	

End point values	furosemide (PP)	torasemide (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	12		
Units: g/m²				
arithmetic mean (full range (min-max))				
LVMI (g/m2)	-24.065546 (-83.80 to 30.20)	-8.930035 (-50.00 to 23.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of the Cardiac structure and function LVEDVI and LAVI

End point title	Change of the Cardiac structure and function LVEDVI and LAVI
End point description:	
LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index;	
End point type	Secondary
End point timeframe:	
9 months	

End point values	furosemide (PP)	torasemide (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	12		
Units: mL/m2				
arithmetic mean (full range (min-max))				
LVEDVI	-1.369978 (-32.80 to 11.00)	8.974017 (-15.00 to 100.00)		
LAVI	11.845524 (-22.00 to 28.00)	-4.433040 (-25.80 to 17.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of the Cardiac structure and function E-wave

End point title	Change of the Cardiac structure and function E-wave
End point description:	
End point type	Secondary
End point timeframe:	
9 months	

End point values	furosemide (PP)	torasemide (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	12		
Units: m/s				
arithmetic mean (full range (min-max))				
E wave	3.227311 (-19.20 to 43.00)	-0.925811 (-33.00 to 22.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of the Cardiac structure and function Deceleration

End point title	Change of the Cardiac structure and function Deceleration

End point description:

End point type	Secondary

End point timeframe:

9 months

End point values	furosemide (PP)	torasemide (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	12		
Units: time in ms				
arithmetic mean (full range (min-max))				
Deceleration time	-0.149871 (-12.00 to 10.00)	-4.746263 (-29.00 to 7.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of the Cardiac structure and function in 6MWT

End point title	Change of the Cardiac structure and function in 6MWT

End point description:

End point type	Secondary

End point timeframe:
9 months

End point values	furosemide (PP)	torasemide (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	12		
Units: distance in m				
arithmetic mean (full range (min-max))				
6MWT distance	-24.065546 (-83.80 to 30.20)	-8.930035 (-50.00 to 23.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory change in Sodium and Potassium

End point title	Laboratory change in Sodium and Potassium

End point description:

End point type	Secondary

End point timeframe:
9 months

End point values	furosemide (PP)	torasemide (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	12		
Units: mmol/L				
arithmetic mean (full range (min-max))				
Sodium	0.848150 (-5.00 to 4.00)	1.051091 (-3.00 to 5.00)		
Potassium	0.146975 (-0.50 to 1.10)	-0.103028 (-1.00 to 0.50)		

Attachments (see zip file)	Graphical display of safety parameters/Figure S1 Graphical

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory Change in Creatinine

End point title	Laboratory Change in Creatinine

End point description:

End point type	Secondary

End point timeframe:

9months

End point values	furosemide (PP)	torasemide (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	12		
Units: mg/dL				
arithmetic mean (full range (min-max))	0.051509 (-0.26 to 0.60)	0.002024 (-0.32 to 0.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory Change in NTproBNP

End point title	Laboratory Change in NTproBNP

End point description:

NT-proBNP, N-terminal pro-B-type natriuretic peptide

End point type	Secondary

End point timeframe:

9 months

End point values	furosemide (PP)	torasemide (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	12		
Units: pg/mL				
arithmetic mean (full range (min-max))				
NT-proBNP	100.427856 (-64.60 to 696.50)	19.663125 (-115.50 to 476.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Quality of life (KCCQ)

End point title	Change in Quality of life (KCCQ)

End point description:

Kansas City Cardiomyopathy Questionnaire

End point type	Secondary

End point timeframe:

9 months

End point values	furosemide (PP)	torasemide (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	12		
Units: Score				
arithmetic mean (full range (min-max))				
KCCQ total symptom	1.844597 (-25.00 to 41.67)	2.262459 (-25.00 to 33.33)		
KCCQ clinical summary	1.168577 (-19.79 to 36.77)	3.951155 (-15.63 to 31.25)		
KCCQ overall summary	3.560723 (-16.93 to 27.08)	-0.038717 (-18.75 to 27.08)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Difference between Furosemide and Torasemide in ITT Group

End point title	Difference between Furosemide and Torasemide in ITT Group

End point description:

End point type	Other pre-specified

End point timeframe:

9 months

End point values	Diff (F–T) ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: ng/ml				
arithmetic mean (standard deviation)				
Percentage PIP change	0.11 (± 25.63)			
Absolute PIP change	1.90 (± 30.70)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

9 months

Adverse event reporting additional description:

One non-cardiac death with no relation to the study drug or procedures was observed in the furosemide group. Overall, 17.1% of patients dropped out due to other causes, mainly refractory congestion requiring intensified therapy outside of the protocol

Assessment type	Non-systematic

Dictionary used

Dictionary name	own
Dictionary version	1

Reporting groups

Reporting group title	Furosemide
Reporting group description: -	
Reporting group title	Torasemide

Reporting group description: -

Serious adverse events	Furosemide	Torasemide	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 18 (61.11%)	11 / 17 (64.71%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Investigations			
fracture, surgery, depression, pulmonary infection			
subjects affected / exposed	5 / 18 (27.78%)	4 / 17 (23.53%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
refractory congestion, cardiac decompensation			
subjects affected / exposed	1 / 18 (5.56%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
acute coronary syndrome, atrial flutter/fibrillation			

subjects affected / exposed	3 / 18 (16.67%)	3 / 17 (17.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 18 (5.56%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
anuresis, acute renal failure			
subjects affected / exposed	1 / 18 (5.56%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Furosemide	Torasemide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 18 (83.33%)	10 / 17 (58.82%)	
Investigations			
Hyperkalaemia (>5.2 mmol/L)			
subjects affected / exposed	1 / 18 (5.56%)	3 / 17 (17.65%)	
occurrences (all)	1	3	
Hypotension (≤100 mmHg systolic blood pressure)			
subjects affected / exposed	1 / 18 (5.56%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Injury, poisoning and procedural complications			
Falls			
subjects affected / exposed	2 / 18 (11.11%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Refractory congestion			
subjects affected / exposed	2 / 18 (11.11%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Renal and urinary disorders			

Worsening renal function (> 0.3mg/dL increase in Creatinine)			
subjects affected / exposed	9 / 18 (50.00%)	3 / 17 (17.65%)	
occurrences (all)	9	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2014	#1 Amendment: Update protocol V1.3. from 2013/08/07 Modul 1
02 March 2015	#2 Amendment: Update study protocol + Synopse V1.3
24 August 2015	#3 Amendment: Update study protocol V1.4 from 2015/ 08/06, update Modul 1
05 April 2016	#4 Amendment: Change manufacturer of study medication., update Modul 1 - IMPD, SmPC

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28891228